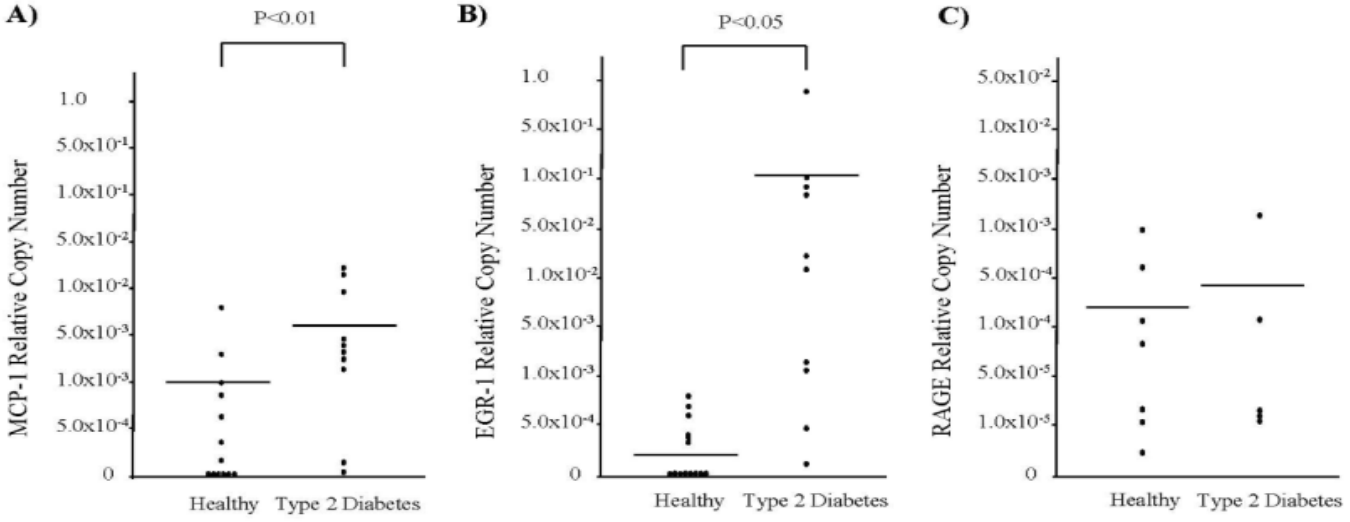
Type 2 Diabetes and Vascular Disease in Human Studies: The Interplay of Systemic Endothelial Activation and Inflammatory Cell Stress during Disease Progress

Background: Type 2 diabetes (T2D) is a major accelerator of macrovascular disease and its complications. Chronic vascular inflammation may play a role in the development of macrovascular complications in diabetic patients. We validated an innovative and minimally invasive approach that allows collection of vascular endothelial cells and characterization of their molecular phenotype in human subjects. By using this novel endothelial sampling and Real-Time PCR techniques, we examined the association of endothelial expression of three inflammatory mediators; Early Growth Response-1 (EGR-1, receptor for advanced glycation end products (RAGE) and monocyte chemoattractant protein-1 (MCP-1) with Type 2 Diabetes. **Methods:** Endothelial samples are obtained from the venous endothelium of 10 T2D patients (59±10 yrs old) with elevated HbA1c (> 8.5 %) and macrovascular complications and 17 age-and gender matched healthy volunteers (55±12 yrs old) using five guide wires sequentially inserted through a 20-gauge angiocatheter. Endothelial cells are purified using magnetic beads with adsorbed CD146 antibody and subjected to RNA amplification. Amplified RNA was analyzed by Real-Time PCR for EGR-1, RAGE and MCP-1 transcripts. **Results:** Real-Time PCR analysis reveals gene expression patterns in patient-derived endothelial cells We showed that vascular disease was associated with significant induction of pro-inflammatory genes: MCP-1 (5-fold), EGR-1 (460-fold), and RAGE (1.6-fold) in the venous endothelium of T2D patients vs age-matched healthy volunteers (Figure).**Conclusion and Ongoing Studies:** By a minimally invasive, safe, and reliable technique, vascular inflammation can be monitored in human subjects. Expression of genes implicated in the atherosclerotic process is increased in the venous endothelium of patients with T2D and arterial vascular disease. Our results suggest venous endothelium chronicles systemic activation of endothelial in patients with T2D and macrovascular complications. This activation may present initially low levels of endothelial inflammation and may give rise to a self-sustaining circuit of vascular inflammation in case of poorly controlled hyperglycemia, by attracting/activating leukocytes and by activation of interacting signaling pathways. We currently enroll subjects to investigate when and how this inflammation starts and whether it involves leukocytes in the setting of the vascular inflammation. We will compare the "activated" phenotype of endothelial cells and leukocytes by global gene expression of selected oxidative/inflammatory programs relevant to "hyperglycemia" and to "the vascular complications" of endothelial cells in patients with T2D at different disease stages vs controls and will attempt to link it to hyperglycemia, vascular complications and oxidative stress. This work may lead to approaches to detect early endothelial dysfunction in T2D and response to therapies.



A) MCP-1 B) EGR1 C) RAGE